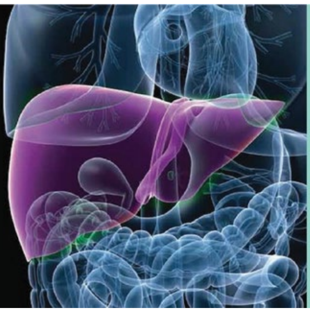

Risk of Nonsteroidal Anti-inflammatory Drugs and Safety of Acetaminophen in Patients with Advanced Liver Disease

Miguel H. Malespin, M.D.

Several factors have contributed to misconceptions regarding nonsteroidal anti-inflammatory drug (NSAID) and acetaminophen use in patients with advanced liver disease. NSAIDs are commonly recommended as first- or second-line therapy for pain management by several societies and organizations. Their use remains uncontrolled, and the vast array of over-the-counter agents lend to a preconceived notion that NSAIDs are generally safe. Furthermore, awareness of acetaminophen toxicity as a common cause of acute liver failure has resulted in distortions regarding the safety and tolerability of these drugs in patients with advanced liver disease.

NSAID AND ACETAMINOPHEN SAFETY IN LIVER DISEASE

There exist a variety of nonselective cyclo-oxygenase (COX) inhibitors (Table 1) with a broad range of indications, including primary and secondary prevention of cardiovascular (CV) disease and treatment of certain rheumatological conditions.[1,2] Other antipyretic, anti-inflammatory, and analgesic effects exist through inhibition of inflammatory prostaglandin synthesis (Fig. 1). Since its discovery in the late 19th century, aspirin (ASA) remains among the most commonly used analgesic products worldwide.[3]

Salicylates and other NSAIDs are highly bound to albumin, undergo hepatic metabolism by cytochrome P_{450} (CYP450) enzymes, and release byproducts that predominantly undergo renal excretion.[4,5] Thus, a decrease in hepatic function can lead to an alteration in the processing of NSAIDs and predispose individuals to inherent risks that exist in regard to gastrointestinal (GI) mucosal injury, bleeding, and renal disease.

Abbreviations: ASA, aspirin; COX, cyclo-oxygenase; CYP450, cytochrome P_{450}; GI, gastrointestinal; NAPQI, *N*-acetyl-*p*-benzoquinone imine; NASH, nonalcoholic steatohepatitis; NSAID, nonsteroidal anti-inflammatory drug.

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TABLE 1. COMMERCIALLY AVAILABLE NSAID AGENTS

Irreversible Nonselective	Reversible Nonselective	COX-2 Inhibitors
ASA	Ibuprofen	Celecoxib
Salsalate	Naproxen	Etoricoxib
Choline magnesium trisalicylate	Indomethacin	
Diflunisal	Diclofenac	
	Meloxicam	
	Sulindac	
	Ketoprofen	
	Etodolac	
	Tolmetin	
	Flurbiprofen	
	Oxaprozin	
	Piroxicam	
	Meclofenamate	
	Mefenamic acid	
	Nabumetone	

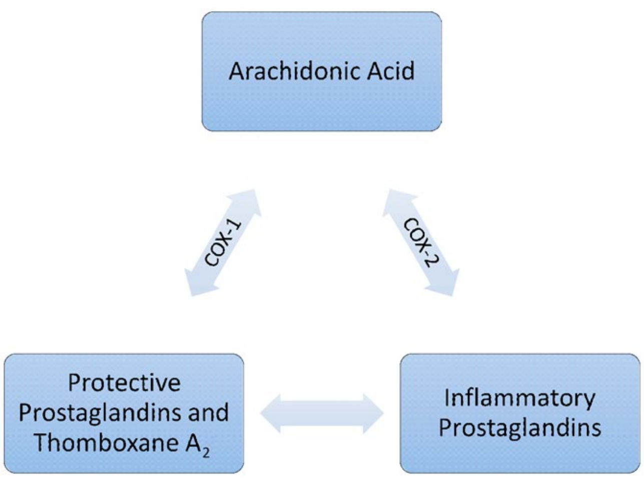

FIG 1 COX enzyme pathways.

GI TOXICITY OF NSAIDS

Prostaglandins and nitric oxide are essential compounds that play a central role in maintaining GI mucosal integrity through protective and repair mechanisms (Fig. 1). NSAID-induced mucosa GI injury can range from mild gastritis to the development of complicated peptic ulcer disease (Fig. 2). The risk for portal and nonportal hypertensive bleeding

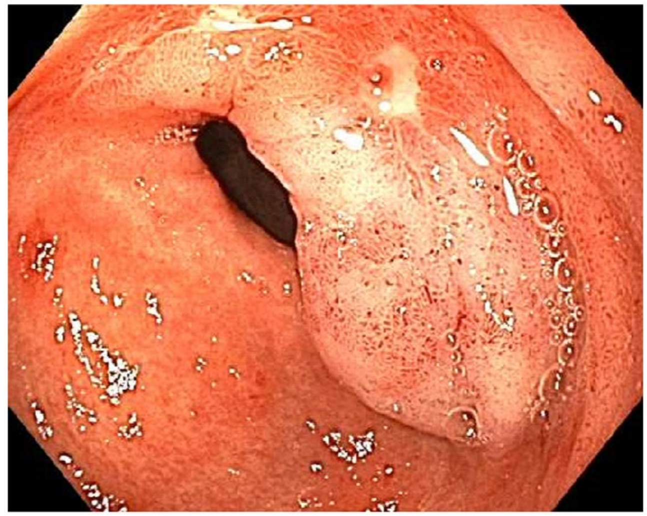

FIG 2 Gastric ulcer secondary to chronic NSAID use.

is further increased as a result of decreased platelet aggregation stemming from a reduction in thromboxane A_2 production and can be further augmented by coexisting coagulopathy and thrombocytopenia.[6,7] Thus, patients and providers must exercise cautionary use of NSAIDs given the increased risk for GI bleeding in patients with cirrhosis and particularly in those with portal hypertension.

RENAL TOXICITY OF NSAIDS

Maintenance of adequate renal function is crucial in patients with cirrhosis complicated by portal hypertension. The development of arterial splanchnic vasodilation leads to a decrease in the effective circulating volume and organ perfusion. Activation of the renin-angiotensin system further promotes adequate perfusion by promoting renal vasoconstriction and increasing cardiac output.[8] Local release of prostaglandins promotes a vasodilatory effect, thus maintaining renal homeostasis.[9] Although the deleterious effects of short-term NSAID use are generally reversible, the degree to which a decrease in renal function occurs is largely dependent on the severity of liver disease and the ability of the drug to inhibit prostaglandin synthesis (indomethacin > ibuprofen > ASA).[9]

Activation of the renin-angiotensin systems also promotes renal sodium and fluid reabsorption.[8] Sodium restriction along with diuresis-natriuresis with furosemide and spironolactone remain as mainstays for the initial management of ascites. The vasoconstrictive properties of NSAIDs lend to an inability to adequately maintain appropriate natriuresis and thus reduce the efficacy of diuretics.[9] Therefore, inadvertent NSAID use should be considered in patients with resistant ascites and sodium excretion ≤78 mEq/day on a 24-hour urine collection.[10]

COX-2 INHIBITORS

COX-2 inhibitors (celecoxib) are able to provide comparable analgesic effects with a reduction in the GI and renal adverse effects of nonselective COX inhibitors. These drugs have been associated with increased CV risks, leading to a withdrawal of some COX-2 inhibitors. Animal and small-scale human studies have thus far shown short courses of COX-2 inhibitors as a safe alternative in patients with cirrhosis requiring analgesia.[11] Given the scarcity of large-scale data, the use of COX-2 inhibitors is not recommended in patients with cirrhosis.

ASA IN NONALCOHOLIC STEATOHEPATITIS

Although it is generally recommended that patients with cirrhosis abstain from use of ASA and other NSAIDs, it must be recognized that patients with nonalcoholic steatohepatitis (NASH) have an inherent increased risk for cardiac disease and stroke. Thus, there remains a role for the use of ASA and other antiplatelet agents in the secondary prevention of CV disease. Risks related to chronic ASA use in persons with NASH who do not have cirrhosis are similar to the general population. On the contrary, risks and benefits of antiplatelet therapy must be weighed in patients with NASH cirrhosis, particularly if there is a prior history of GI bleeding, renal disease, or ascites.

ACETAMINOPHEN USE IN PATIENTS WITH ADVANCED LIVER DISEASE (PARACETAMOL)

Acetaminophen-induced hepatotoxicity represents one of the most common causes of acute liver failure worldwide. Coincidentally, this has led to a general misconception regarding the safety of acetaminophen in patients with advanced liver disease. It has been presumed that decreased glutathione stores in these patients may lead to increased levels of the hepatotoxic intermediate *N*-acetyl-*p*-benzoquinone imine (NAPQI) (Fig. 3). Although large-scale prospective studies are lacking, these pharmacokinetic changes have historically not led to clinically significant adverse events when daily dosage levels are kept at less than 2 g/day.[12] Despite these findings, acetaminophen should be used judiciously in patients with chronic alcohol abuse given a proposed increased risk related to CYP450 induction in conjunction with reduced glutathione stores.

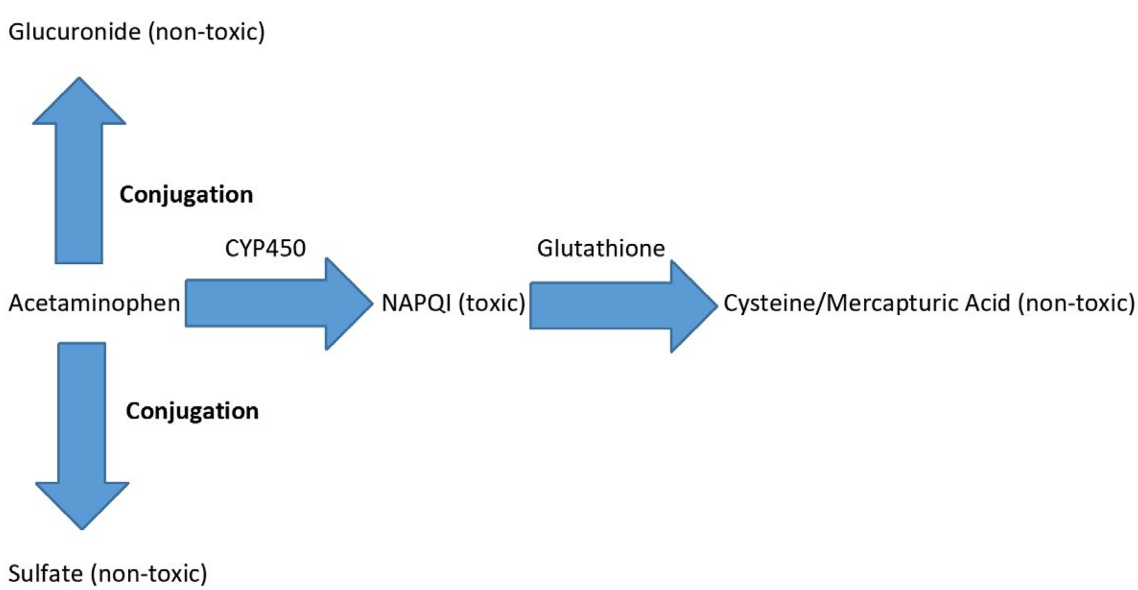

FIG 3 Hepatic acetaminophen metabolism.

SUMMARY

Analgesic management oftentimes begins with the use of over-the-counter therapies, including NSAIDs and acetaminophen. There is a general apprehension that exists regarding acetaminophen use in patients with advanced liver disease given the association between acetaminophen overdose and acute liver failure. Yet it has been proven that short courses of acetaminophen with a maximum dosage of 2 g/day are safe and preferred for patients with advanced liver disease and without chronic alcohol abuse. NSAIDs are not recommended given an increased susceptibility to development of adverse effects related to COX-1 inhibition. Patients with NASH cirrhosis are at increased CV risk and may require low-dose ASA for secondary prevention of CV disease. Careful monitoring of potential renal-related and GI side effects is required in this population.

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